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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,440	01/10/2002	Costas D. Maranas	P05468US1	1336

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MCKEE, VOORHEES & SEASE, P.L.C.  
ATTN: PENNSYLVANIA STATE UNIVERSITY  
801 GRAND AVENUE, SUITE 3200  
DES MOINES, IA 50309-2721

EXAMINER
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MORAN, MARJORIE A

ART UNIT	PAPER NUMBER
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1631

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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<b>Office Action Summary</b>	Application No. 10/043,440	Applicant(s) MARANAS ET AL.	
	Examiner Marjorie Moran	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 02 February 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-8, 10-16, 19-27, 30-33 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-8, 10-16, 19-27 and 30-33 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

The amendment filed 2/2/07 has been entered. Claims 1-8, 10-16, 19-27 and 30-33 are pending. All objections and rejections not reiterated below are hereby withdrawn in view of the amendment and arguments filed 2/2/07.

### ***Claim Objections***

Claim 21 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 21 is directed to a system but depends from claim 20, which recites a method. Claim 21 therefore does not further limit the METHOD of claim 20. For purposes of further examination, claim 21 is interpreted as if it recited "The method of claim 20..." It is noted that claim 21 formerly recited "The method of claim 20..." and was NOT previously objected to.

### ***Claim Rejections - 35 USC § 101***

Claim 19 is directed to a system comprising a model contained on a computer readable medium, a plurality of logic constraints, and commands. In view of applicant's comments on page 16 of the response filed 2/2/07, the system is interpreted to be a "computer component" comprising a computer-readable medium containing a model and commands for producing an altered model. Although it is unclear what the actual relationship between elements is intended to be (see below), the system is limited to comprise a physical element and is therefore statutory.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 21, and 22 are again rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The limitation that “at least a subset” of logic constraints are capable of protecting against violation of a kinetic barrier, as recited in amended claims 2 and 21, is also new matter. Original claim 2 recite selection of constraints to protect against violation of a barrier, but did not limit the selection to be for “at least a subset.” The originally filed specification does not provide support anywhere for a “at least a subset” of constraints which protect against violation of a kinetic barrier. In the response filed 7/28/06, applicant does not point to support for the newly recited limitation, and none is apparent, as set forth herein, therefore claims 2 and 21 are also rejected for this reason.

Applicant's arguments filed 2/2/07 have been fully considered but they are not persuasive. On pages 23-24 of the response, applicant argues that the originally filed specification, on pages 57-58, discloses connectivity restraints which are added by

partitioning reactions into subsets and identifying the smallest set of reactions “capable of ensuring *adequate* connectivity” between external metabolites and a biomass (emphasis added by examiner). This is not a full and complete disclosure of “at least a subset of logic constraints which are capable of protecting against violation of a kinetic barrier” as recited in the instant claims. Logic constraints which are capable of protecting against violation of a kinetic barrier are not new matter; however, there is no disclosure for a subset of these particular constraints. A disclosure such as that set forth on pages 57-58 that *reactions* may be divided into subsets is not a disclosure for a subset of *constraints* which protect against violation of a kinetic barrier. For these reasons, the arguments are not persuasive and the rejection is maintained.

Logic constraints which include “DNA experimental data constraints,” as recited in claim 22, are new matter. Original claims 1 and 19 limited constraints to include “differential DNA microarray experimental data constraints.” The originally filed specification also discloses “differential DNA microarray experimental data constraints” in various places. As argued by applicant on page 24 of the response filed 2/2/07, the specification does disclose, on pages 7-9, that constraints may include “DNA microarray experimental data.” This is not supportive of the broader limitation recited in claim 22, therefore applicant’s argument is not persuasive. Nowhere do the original claims or specification recite or disclose “DNA experimental data constraints” which are NOT derived from “microarray” experiments. As the limitation recited in claim 22 is different in scope than that originally disclosed/recited, the examiner maintains that claim 22 recites new matter, and the rejection is maintained.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16, 19-27, 29-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 6, 19, 23, 29, and 33 recite in each preamble "modeling cellular metabolism of an organism" but the steps/instructions of the claims fail to recite any relationship of an FBA model to an organism. As it is unclear what relationship is intended between the preamble of each claim and the actual steps/limitations recited, the claims are indefinite. Claims 2-5, 7, 8, 10-16, 20-22, and 24-27 depend from one of claims 1, 6, 23, and 29, and fail to overcome the indefiniteness of the parent claims, and are therefore also indefinite.

Applicant's arguments filed 2/2/07 have been fully considered but they are not persuasive. In response to the argument that addition of the phrase "of a metabolic network" clarifies that the FBA model is one of a metabolic network of an organism, it is noted that a model of a metabolic network may be constructed for an individual cell or organ and does not necessarily require that the model represent a network for the entirety of an organism. None of the claimed steps/commands limits the FBA model and/or the metabolic network to be one for/derived from an organism. As the relationship of the FBA model to an organism is still unclear, the rejection is maintained.

Claims 16 and 32 recite that a change is to be engineered in an organism “based on” a desired metabolic outcome. The relationship between the engineered change and the desired metabolic outcome intended by the phrase “based on” is unclear.

Specifically, it is unclear whether the engineered change is intended to cause or result in the desired metabolic outcome in the organism or is merely a change having some unspecified degree of relationship to metabolism. As it is unclear what is intended by the phrase “based on”, the claims are indefinite.

Applicant argues in the response filed 2/2/07 that “the engineered change is based on the desired metabolic outcome of the model.” This does not clarify the phrase as it is still unclear what relationship is intended between the engineered change and the desired metabolic outcome; i.e. whether the change is engineered to PRODUCE or RESULT IN the desired metabolic outcome by or in the organism, or whether the change merely has some undefined relationship to the desired metabolic outcome. For example, the desired metabolic outcome is 100% increase in production of a protein. If an increase of only 30-50% is achieved in the “engineered” organism, is the engineered change still one which is “based on” the desired metabolic outcome even though that outcome is not actually achieved? What amount of increase would be required for that change to be “based on” the desired metabolic change? As the phrase “based on” still renders the claims unclear, the rejection is maintained.

Claim 30 recites the phrase “the flux balance analysis model of the organism” in the last two lines. There are at least two flux balance analysis models recited previously in the claim, but no flux balance analysis model specific to an organism is recited

anywhere in the claim. It is unclear whether the antecedent basis for "the flux balance analysis model of the organism" is intended to be the FBA model constructed in the first step of the claims or the altered model (i.e. the model having improved predictive capabilities) or whether some other model is intended, therefore the claim is indefinite. Claims 31 and 32 depend from claim 30 and are therefore also indefinite.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-8, 12-15, 19, 22-23, 25-27, 30, 31 and 33 are rejected under 35 U.S.C. 102(e) as being anticipated by PALSSON at al. (US 2002/0012939, filed 2/2/1999).

PALSSON teaches modeling cellular metabolism utilizing stoichiometric mass balances (para's 31-34), and teaches application of constraints (para's 40-45) which result in a restricted (tightened) model (para 40), wherein the constraints may be applied to change a flux boundary to thereby produce an improved model (para 43), thereby anticipating claims 1, 6, 19, 23, and 33. These constraints may include those which are required to meet maintenance requirements with regard to energy (kinetic)



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requirements; i.e. prevent violation of a kinetic barrier/boundary (para 43) or may include “connectivity” constraints; i.e. constraints including information with regard to connections between fluxes inside and outside the cell (para 45); thereby anticipating claims 2-3, 7, 21, and 25. PALSSON specifically teaches that by adjusting constraints, it is possible to optimize the flux distribution through the metabolic network (para’s 47 and 57-59); i.e. to improve/optimize the predictive capabilities of the model as it applies to the metabolic network. The constraints are those which relate reaction fluxes and metabolic concentrations of analytes in a network (para 45), therefore claim 8 is anticipated. PALSSON also teaches use of mixed integer linear programming (para’s 44-46), use of differential DNA microarray data (para 60), and solving for desired metabolic outcomes (para 41 and Examples, pp. 5-6), thereby anticipating claims 4-5, 14-15, 19, 22, 26-27, and 30-31. PAULSSON teaches determination of minimal media for growth of an organism, which is inherently a teaching for identifying a minimal set of metabolic reactions (para 61), and teaches determining the effect of “deletions” in his model (Example 2, p. 6), which is also inherently a teaching for calculating a minimal set of reactions necessary for growth, which teachings anticipate claims 12-13.

Applicant's arguments filed 2/2/07 have been fully considered but they are not persuasive. It is noted that applicant admits on pages 30-31 of the response that PALSSON application of constraints in FBA models of metabolic processes. In response to the argument that PALSSON's constraints are not “logic constraints,” applicant's attention is directed to para's 54 and 59 wherein constraints placed on the

network are defined by a relationship between the amount of a substrate (metabolic concentration) and specific uptake rates (reaction fluxes), as recited in claim 8. As the description of PALSSON's constraints meets the definition recited in the claims, the examiner maintains that PALSSON's constraints are logic constraints. The argument that the constraints are applied in combination with linear equations is moot as the instant claims do not recite that linear equations can not be used in formulation an FBA model and/or applying constraints. In fact, claims 12 recites applying a computational procedure, and claims 4, 14, and 26 recite applying mixed integer linear programming (another computational procedure), therefore it is clear that the claims do NOT exclude use of computations, such as the linear equations taught by PAULSSON, in combination with constraints, as applied to an FBA model. Arguments with regard to stoichiometric boundaries and a regulation matrix are also moot as the instant claims do not recite limitations regarding stiochiometric boundaries or a regulation matrix.

For the reasons set forth above, applicant's arguments are not persuasive and the rejection is maintained.

### ***Conclusion***

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie Moran whose telephone number is 571-272-0720. The examiner can normally be reached on M-F 6:30 am- 2 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marjorie Moran  
Primary Examiner  
Art Unit 1631

*Marjorie A. Moran*  
4/14/07